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**HiTSelect: a comprehensive tool for high-complexity-pooled screen analysis.**

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**Funding Grants:** Genetic dissection of human cellular reprogramming to pluripotency

**Public Summary:**

The analysis of gene function in stem cells is of fundamental importance to devise the best new therapies in the context of Regenerative Medicine. This article reports a novel methodology for analyses of large-scale genetic screens in stem cells.

**Scientific Abstract:**

Genetic screens of an unprecedented scale have recently been made possible by the availability of high-complexity libraries of synthetic oligonucleotides designed to mediate either gene knockdown or gene knockout, coupled with next-generation sequencing. However, several sources of random noise and statistical biases complicate the interpretation of the resulting high-throughput data. We developed HiTSelect, a comprehensive analysis pipeline for rigorously selecting screen hits and identifying functionally relevant genes and pathways by addressing off-target effects, controlling for variance in both gene silencing efficiency and sequencing depth of coverage and integrating relevant metadata. We document the superior performance of HiTSelect using data from both genome-wide RNAi and CRISPR/Cas9 screens. HiTSelect is implemented as an open-source package, with a user-friendly interface for data visualization and pathway exploration. Binary executables are available at <http://sourceforge.net/projects/hitselect/>, and the source code is available at <https://github.com/diazlab/HiTSelect>.

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